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Ability of a preterm surveillance clinic to triage risk of preterm birth: a prospective cohort study

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Abstract

Objective

To identify whether preterm surveillance clinics accurately risk-stratify high-risk women, by comparing outcomes of those admitted into hospital on the basis of asymptomatic testing to those not admitted.

Method

We performed a subanalysis from a larger prospective cohort study of ultrasonic cervical length, quantitative fetal fibronectin (qfFN), and risk of spontaneous preterm birth. We identified 1130 asymptomatic singleton pregnancies at high risk of preterm birth, screened between 23 and 28 weeks of gestation at a preterm surveillance clinic (PSC) at a tertiary hospital in London, UK. Gestational age at delivery and proportion of preterm births <30 weeks, with neonatal outcomes, were compared between those admitted electively when asymptomatic and all others.

Results

66 (4%) were admitted to hospital from clinic following asymptomatic screening (inpatient group). The mean gestation at delivery for those not electively admitted (outpatient group) was term, significantly higher than those admitted from PSC (38.4 vs 32.1 weeks, $p<0.0001$). Preterm births <30 weeks were rare in the outpatient group relative to those admitted (1.32% vs 36.4%, $p<0.0001$). The neonatal mortality was 0.188% in the outpatient group compared to 4.55% in those electively admitted ($p<0.0001$). Other complications such as neonatal deaths, APGAR scores SCBU/NICU admissions, respiratory distress syndrome, interventricular haemorrhage and low birth weights were significantly lower in patients managed as outpatients.

Conclusion

Preterm surveillance clinic using cervical length and fFN accurately risk triage asymptomatic high-risk pregnant women. Women at highest risk of adverse outcome can be identified for elective admission to hospital and appropriate management.

Introduction

The clinical burden of preterm birth is substantial. 7.4% of infants are born under 37 weeks and 57% of neonatal deaths are attributed to preterm birth and its consequences [1]. Knowledge of multiple clinical risk factors is insufficient to accurately predict preterm labour [2] and allow for prophylactic interventions such as antenatal steroids, progesterone, cerclage, and in-utero transfer to be efficiently targeted [3-5]. Hospitalization is only justified in patients deemed at high risk of imminent delivery and poor outcomes. Despite this a large majority of women admitted to hospital deemed at risk of preterm birth do not deliver within 7 days [6]

Cervical length ultrasound surveillance is an established method of screening those women without symptoms of preterm labour (asymptomatic) but deemed high-risk and aims to identify those who might benefit from a cervical cerclage [7]. However cervical insufficiency is likely to represent only one factor in the aetiology of preterm birth as more than 50% of those with a short cervix deliver beyond 35 weeks [8].

A range of biochemical bedside tests are available to help distinguish those at most risk of preterm labour [9]. Fetal fibronectin (fFN) is the most widely used in the UK [10]. In asymptomatic high risk women, it has a negative predictive value for spontaneous preterm birth before 30 weeks of 98.6% and a positive predictive value of 13.6% (using the conventional fFN threshold of 50ng/mL). [11] When combined with cervical length and clinical history, fFN prediction is enhanced further [12, 13]

The Preterm Surveillance Clinic (PSC) at St Thomas' Hospital, London, UK, combines clinical history, ultrasonic cervical length measurements and fFN to screen

women with risk factors for preterm birth. Those triaged as low-risk are managed as outpatients (unless they present clinically with symptoms) whilst those thought at highest risk of preterm birth, based on screening tests are admitted into hospital for observation and prophylactic interventions. The purpose of this study was to identify whether the PSC accurately risk-stratifies asymptomatic high-risk women, by comparing neonatal outcomes of those not routinely admitted, compared to those admitted into hospital from the PSC on the basis of asymptomatic testing.

Methods

This was a sub-analysis of a large observational study (Evaluation of Fetal Fibronectin with a Quantitative Instrument for the Prediction of Preterm birth) conducted at St Thomas' Hospital (London, United Kingdom). Written informed consent was obtained from all participants. Women with singleton pregnancies, not symptomatic but at risk of preterm birth between 23+0 and 28+0 gestational age attending the PSC from 1 October 2010 to 30 June 2015 were selected for this sub-analysis. The women also had to meet at least one of the inclusion criteria: history of previous late miscarriage (16 to 23+6 weeks), previous preterm birth (<37 weeks), previous preterm premature rupture of membranes (PPROM) (<37 weeks,) previous cervical surgery (eg LLETZ, cone biopsy), uterine abnormalities, and/or cervical length <25mm by transvaginal ultrasound). Results from women with vaginal bleeding, PPRM, multiple pregnancy, cervical dilation of 3 cm or greater, were

excluded from the analysis. Gestational ages were confirmed with standard early ultrasound scans.

Both fFN and cervical length measurements were used in conjunction with clinical history to risk assess, using methodology defined elsewhere [11] Women at low-risk following these assessments were discharged from the clinic between 22 and 24 weeks. Women deemed high-risk were admitted and managed according to local protocols as described in Figure 2.

The data were retrieved from October 2010 to June 2015. The search yielded a group of 1253 women eligible for analysis. The exclusions flow diagram is shown in Figure 1. We excluded 123 women, as there were inadequate outcome data available. Thus, the total number of women who underwent analysis was 1130. From this group, we then identified 66 women who had been admitted to hospital at least once on any of their visits (when asymptomatic) between the eligible gestational period as a result of their screening test results (poor obstetric history, fFN positive and CL <15mm). The clinic policy was to admit only if the fFN was >50ng/mL and the cervical length was <15mm, but ultimately this was at the discretion of the senior obstetrician in clinic. The remaining 1064 women were managed as outpatients by PSC, the outcomes of which were compared to those who were admitted, regardless of whether they were subsequently admitted for clinical reasons.

The main outcomes identified and compared between the two groups were gestational age at delivery, stillbirth, neonatal admission to SCBU or NICU, neonatal death, birthweight, respiratory distress syndrome, intraventricular haemorrhage and Apgar

score at 5 minutes. Stillbirth was defined as the death of a baby before or during birth after 24 weeks of gestation. Neonatal death was defined as any deaths occurring within the first 28 days of life.

Statistical methods

Data were analysed descriptively and inferentially using Graphpad PRISM 6.0 statistics software. Proportions are presented with 95% exact binomial confidence intervals (CI).

The primary outcomes were mean gestational age and a delivery gestation <30 weeks. Gestational age at delivery was analysed as a continuous variable and gestational age at delivery <30 weeks was analysed as a nominal variable.

Secondary outcomes were delivery <34 weeks and <37 weeks and mean birthweight. All categorical (nominal) variables were compared using chi-square with the statistical significance set at $p < 0.001$ to account for the multiple hypothesis testing. Student T test was used to calculate the average maternal ages, average weeks of gestation at delivery and average birthweights.

Results

The characteristics of the outpatient and inpatient groups are summarised in Table 1. The previous cervical surgery rate, previous preterm birth rate and previous PPROM rate were higher in outpatient group. The rate of previous second trimester miscarriage was higher in the inpatient group.

Table 2 summarises the outcomes for the outpatient and inpatient groups. Those patients admitted when asymptomatic from the PSC were significantly more likely to deliver before 30 weeks (RR 27.6) than those patients who were not admitted from PSC. Those discharged had low rates of preterm birth before 30weeks (1.32%), in spite of their risk factors and comparable to background risk in England and Wales (1.2% <31/40) [1]. The mean gestation at delivery for those managed as outpatients was 38.4 ± 2.5 weeks compared to 31.9 ± 5.6 weeks for those admitted from PSC ($p < 0.0001$).

The secondary outcomes of rates of delivery gestation <34 weeks and <37 weeks, neonatal deaths, stillbirths, APGAR <7, intraventricular haemorrhage, and NICU/SCBU admissions were all significantly lower amongst those women managed as outpatients by PSC. The mean birthweights of neonates born to women admitted from PSC were significantly lower ($1.98\text{kg} \pm 2.93$ vs $3.21\text{kg} \pm 0.64$, $p < 0.0001$)

In the outpatient group, one of the four stillbirths had an emergency LSCS at 24 weeks. The remaining 3 stillbirths were not linked to preterm labour –one was an intrapartum term stillbirth and two were associated with major congenital abnormalities (see table 2). There was one preterm neonatal death in the outpatient

group, in which a woman with severe pre-eclampsia suffered a placental abruption and the baby died one hour after birth. The other neonatal death in the outpatient group was at 39 weeks and the infant had major cardiac abnormalities.

In the inpatient group all of the stillbirths were associated with extreme prematurity (<25 weeks), spontaneous onset of labour and chorioamnionitis. There were three neonatal deaths in the inpatient cohort, all of which were contributed to by extreme prematurity. One infant delivered at 24 weeks and died 2 days after birth, one delivered at 23+6 but also had multiple congenital abnormalities, and the last delivered at 25+5 weeks and was complicated by sepsis and multiple pulmonary haemorrhages.

Discussion

Whilst there is existing evidence that combined ultrasonic cervical length screening and fFN assists in prediction of preterm birth in asymptomatic women [13, 14], to our knowledge, this is the first study into whether a PSC is appropriately triaging high-risk women. The low incidence of preterm birth and the lack of neonatal complications in those patients not admitted from PSC, suggests appropriate selection of those not requiring admission or further interventions and justifies the policy of discharging from clinic at or before 24 weeks gestation.

The similar prevalence of previous preterm labour or PPRM as risk factors in our inpatient and outpatient groups (Table 1) supports the evidence that these risk factors

alone are not good screening tools [2]. The higher incidence of previous second trimester miscarriage in the inpatient group suggests that these women are more likely to have abnormal tests and worse outcomes.

Detailed analysis of the outpatient perinatal mortality emphasises the ability of the PSC to identify those not at risk of poor outcomes associated with preterm birth. The low stillbirth rate of 0.4%, only includes one case in which prematurity was a contributing factor (the remaining two had major congenital abnormalities). Similarly, one of the neonatal deaths was at term, and the other, whilst preterm, was associated with pre-eclampsia and placental abruption.

The study's major strength is the prospectively collected detailed data in a large group of high risk women, demonstrating the clinic can accurately risk stratify. This provides high levels of reassurance to those not admitted and/or discharged based on asymptomatic testing.

The interpretation of the results in the high-risk women is limited by the need to establish whether admission itself or the subsequent targeting of interventions is improving outcomes. Given the high morbidity and mortality in this group, and that beneficial interventions such as steroid administration and in-utero transfer are time-sensitive, admission for those at high risk of spontaneous preterm labour as determined by PSC is probably justified in the meantime.

We have previously shown that the ultrasonic cervical length screening and fFN act synergistically and improve risk prediction when used together. Our study supports

their combined use in asymptomatic women to select those at high-risk women for admission to hospital. Although these tests and admissions have a cost, the severity of outcomes, and the ability to target time sensitive interventions known to improve outcomes is likely to justify this practice. Amongst the 1130 high risk women in this study, only 66 (5.8%) were electively admitted. With more than one third of those admitted delivering before 30 weeks and 73% before 37 weeks, interventions such as steroid administration are better justified than women who are given steroids for threatened preterm labour alone, where 60% of pregnancies continue beyond 37 weeks [6]. This suggests that surveillance and targeting of interventions in asymptomatic women is justified.

The low rate of false-negative tests might support adjustments to our screening thresholds for admission (FFN>50 ng/ml and CL<15mm). Recent developments in quantitative fetal fibronectin levels in high risk asymptomatic women, suggest that increasing the fFN threshold from 50 ng/ml to 200 ng/mL doubles the positive predictive value to 26.9 (95% confidence interval 17.5-38.2) with only a 0.4% reduction in negative predictive value (98.6 to 98.2%), i.e. women under 200 ng/ml may be safely discharged. Quantitative fFN also helps discriminate those at low risk with a known short cervix (less than 25mm), with 90% of women delivering after 34 weeks gestation if the fFN is less than 10 ng/m [11]. Combining quantitative fFN with risk factors, cervical length provides exciting opportunities for tailoring prediction to the individual (12).

This large study with prospectively collected data demonstrates that a preterm surveillance clinic admitting asymptomatic women at high-risk of preterm birth, on

the basis of cervical length and fFN, correctly identifies those women most at risk of poor neonatal outcomes. The particularly low rates of perinatal morbidity and mortality in the “outpatient” group provide a high level of reassurance to women with negative screens, in spite of their risk factors, and are likely to reduce unnecessary admissions and interventions.

As our understanding of the relationship between quantitative fetal fibronectin, cervical length and risk factors for prematurity becomes more sophisticated, technologies such as the QUIPP App [12] will support preterm surveillance clinics to refine risk stratification further.

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References

1. Office of National Statistics, *Gestation-specific infant mortality 2013* Office of National Statistics 2014
2. Honest, H., et al., *The accuracy of risk scores in predicting preterm birth--a systematic review*. J Obstet Gynaecol, 2004. 24(4): p. 343-59.

3. Crowley, P., *Prophylactic corticosteroids for preterm birth*. Cochrane Database Syst Rev, 2000(2): p. CD000065.
4. Sanchez-Ramos, L., A.M. Kaunitz, and I. Delke, *Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials*. Obstet Gynecol, 2005. 105(2): p. 273-9
5. Duckitt K, Thornton S, O'Donovan O.P, Dowswell T. *Nitric oxide donors for treating preterm labour* Cochrane Database Syst Rev. 2014 May 8;5:CD002860.
6. Iams, J. D., Newman R.B., Thom E.A., Goldenberg R.L., Mueller-Heubach E., Moawad A., Sibai B.M., Caritis S.N., Miodovnik M., and Paul R.H.. *"Frequency of Uterine Contractions and the Risk of Spontaneous Preterm Delivery."* New England Journal of Medicine 346, no. 4 (2002): 250-255.
7. Groom, K.M, Bennett P.R., Golar M., Thalon A., and Shennan A.H. *Elective cervical cerclage versus serial ultrasound surveillance of cervical length in a population at high risk for preterm delivery*. Eur J Obstet Gynecol Reprod Biol. 2004 Feb 10;112(2):158-61.
8. Watson W.J., Stevens D., Welter S. and Day D. *Observations on the Sonographic Measurement of Cervical Length and the Risk of Premature Birth* Journal of Maternal-Fetal Medicine, Volume 8, Issue 1 1999 P17-19

9. Hezelgrave, N L, Shennan A H, and David A. L. *Tests to Predict Imminent Delivery in Threatened Preterm Labour*. British Medical Journal 350 (2015): h2183.
10. Stock, S. J, Morris R.K., Chandiramani M., Shennan A.H., and Norman J.E. *Variation in Management of Women with Threatened Preterm Labour*. Archives of Disease in Childhood-Fetal and Neonatal Edition 100, no. 3 (2015): F276-F276.
- 11 Abbott, D.S., Hezelgrave N.L., Seed P.T., Norman J.E., David A.L., Bennett P.R., Girling J.C., Chandiramani M., Stock S.J., Carter J., Cate R., Kurtzman J., Tribe R.M, Shennan A.H. *Quantitative fetal fibronectin to predict preterm birth in asymptomatic women at high risk*. J.Obstet Gynecol, 2015;125(5):1168-76
- 12 Kuhrt K., Hezelgrave N., Foster C., Seed P.T., Shennan A.H. *Development and validation of a predictive tool for spontaneous preterm birth, incorporating quantitative fetal fibronectin, in symptomatic women* Ultrasound in Obstetrics & Gynaecology, DOI: 10.1002/uog.14894
13. Bolt, L.A, Chandiramani M., De Greeff A., Seed P.T., Kurtzman J., and Shennan A.H. *The Value of Combined Cervical Length Measurement and Fetal Fibronectin Testing to Predict Spontaneous Preterm Birth in Asymptomatic High-risk Women*. Journal of Maternal-Fetal and Neonatal Medicine 24, no. 7 (2011): 928-932.

Figure legends:

1253 asymptomatic high-risk women seen in PSC between October 1 2010 and June 30 2015 at 23+0 to 28+0 weeks of gestation

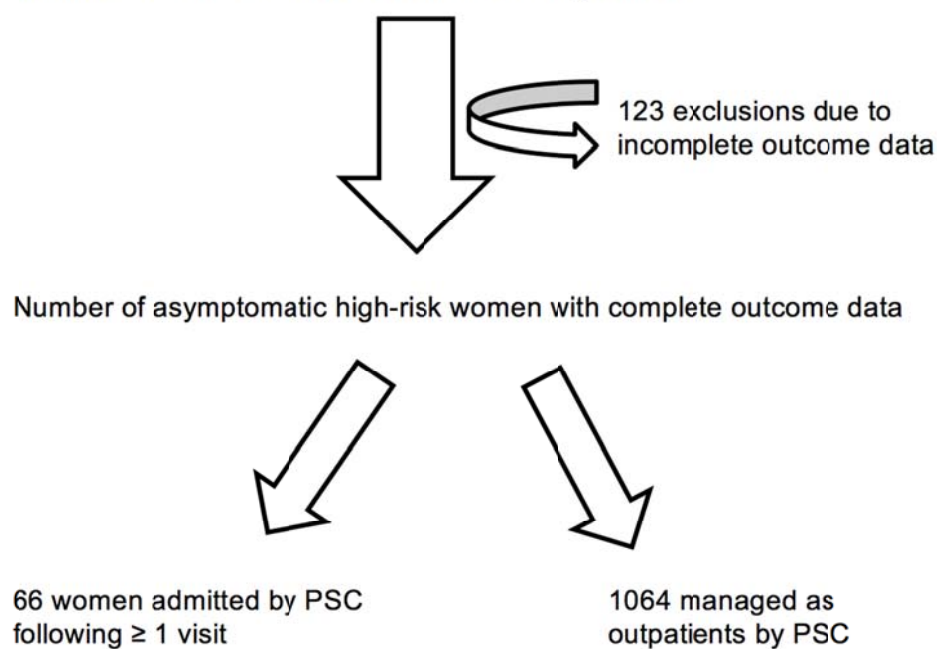


Figure 1. Exclusions flow diagram.

Inpatient management
<p>If infection suspected:</p> <ul style="list-style-type: none">• Urinalysis and MSU• High vaginal swab• FBC and CRP• Appropriate antibiotics <p>Tocolysis (nifedipine) if threatened labour commences, but to enable IUT or corticosteroids administration only</p> <p>Betamethasone (2 doses of 12mg IM 24hours apart, or 12hours apart if delivery imminent)</p> <p>Early discussion with neonatal team and in-utero transfer if necessary</p> <p>Ultrasound for presentation and liquor volume Ultrasound for estimated fetal weight if necessary</p> <p>Vaginal Cerclage if cervical length <25mm and <24weeks</p> <p>Magnesium Sulphate (4g over 20 minutes and then 1g/hr for 24hours) on day of delivery if <30 weeks</p> <p>Benzylpenicillin (GBS prophylaxis) in labour</p>

Figure 2. Inpatient management during study.

Table 1: Baseline Characteristics

	Outpatients N=1064	Inpatients N=66	
Average maternal age (years)	32.8±5.6 (16-48)	32.6±5.1 (21-49)	p = 0.265
Previous preterm birth (%)	36.7 (n=390)	33.3 (n=22)	p=0.55
Previous PPROM (%)	19.5 (n=208)	15.2 (n=10)	p=0.36
Previous second trimester miscarriage (%)	19.8 (n=211)	37.9 (n=25)	p=0.0006
Previous cervical surgery (%)	37.4 (n=398)	18.2 (n=12)	p=0.0014

Table 2: Outcomes for patients admitted from PSC vs those managed as outpatients

	Outpatient (n=1064)	Inpatient (n=66)	RR (95% CI)	p value
<i>Primary outcomes</i>				
Mean gestation at delivery (weeks)	38.4±2.5 (24-42)	31.2±5.6 (23-41)		p<0.0001
Delivery less than <30/40	1.32% (n=14)	36.4% (n=24)	27.6 (15.0-50.1)	p<0.0001
<i>Secondary outcomes</i>				
Delivery <34/40	4.89% (n=52)	57.6% (n=38)	11.8 (8.4-16.5)	p<0.0001
Delivery <37/40	14.0% (n=149)	72.7% (n=48)	5.2 (4.2-6.4)	p<0.0001
Stillbirth rate	0.376% (n=4)	4.55% (n=3)	12.1 (2.8-52.9)	p<0.0001
Neonatal deaths	0.188% (n=2)	4.55% (n=3)	24.2 (4.1-142.2)	p<0.0001
Intraventricular Haemorrhage	0.188% (n=2)	9.09% (n=6)	48.4 (10.0-235.0)	p<0.0001
Respiratory distress syndrome	10.2% (n=108)	56.1% (n=37)	5.5 (4.2-7.3)	p<0.0001
Birthweight Mean (kg)	3.21±0.64 (0.680-5.180)	1.98±2.93 (0.5000-4.562)		p<0.0001
<1kg (ELBW)	0.846% (n=9)	27.3% (n=18)	32.2 (15.1-69.0)	p<0.0001
<1.5kg (VLBW)	1.79% (n=19)	36.4% (n=24)	20.4 (11.8-35.2)	p<0.0001
<2kg	4.70% (n=50)	53.0% (n=35)	11.3 (7.9-16.1)	p<0.0001
<2.5kg (LBW)	11.4% (n=121)	65.2% (n=43)	5.7 (4.5-7.3)	p<0.0001
SCBU/NICU admission	10.2% (n=108)	56.1% (n=37)	5.5 (4.2-7.3)	p<0.0001
APGARS <7	1.50% (n=16)	12.1% (n=8)	8.1 (3.6-18.1)	p<0.0001